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(Commemoration Issue Dedicated to Professor Sango Kunichika On the Occasion of his Retirement)

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Syntheses of Some Derivatives of 1,4-Dioxane and 1,3-Dioxolane

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A convenient route to 2,3-diamido-1,4-dioxanes, 4,5-diamido-2-methyl-1,3-dioxolanes, or 2-alkoxy-4,5-diamido-1,3-dioxolanes starting from carboxylic acid amides via *N,N'*-(1,2-dihydroxyethylene)bisamides was offered.

Diamino-1,4-dioxanes and diamino-1,3-dioxolanes would be interesting bifunctional compounds having moderately water-soluble properties, but no description related to their preparations has been found. In the present paper, we wish to describe a convenient route to diamido-1,4-dioxanes and diamido-1,3-dioxolanes starting from carboxylic acid amides *via N,N'*-(1,2-dihydroxyethylene)bisamides.

Syntheses of *N,N'*-(1,2-dihydroxyethylene)bisamides and *N,N'*-(1,2-dialkoxyethylene)bisamides. At first, the dihydroxybisamides were prepared by the reaction of amides with glyoxal in the presence of a small amount of NaHCO₃, according to the procedure by Vail *et al.*^{1,2)} The results are summarized in Table 1. An attempt to prepare the bisamide from 2-naphthamide or phthalimide resulted in failure, and this may be attributed to the bulkiness of 2-naphthamido and phthalimido groups (see run 8 and 9 in Table 1). Yoshizawa and Taguchi³⁾ succeeded in isolation of two stereoisomers (*dl*- and *meso*-form) of *N,N'*-(1,2-dihydroxyethylene)bisacrylamide prepared from acrylamide, but failed in separation for a homolog, *N,N'*-(1,2-dihydroxyethylene)bismethacrylamide. Our attempts to separate the stereoisomers for several dihydroxybisamides by application of various techniques were also unsuccessful.

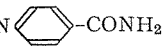
Some of the dihydroxybisamides were converted to the corresponding dialkyl ethers by the action of alcohols containing trace amounts of *p*-toluenesulfonic acid or H₂SO₄. Ruggli and his co-workers⁴⁾ formerly suggested the formation of two stereoisomers of *N,N'*-(1,2-diethoxyethylene)bisbenzamide (3b) (their melting points were 190–191°C and 219°C). We also succeeded in separation of two stereoisomers having different physical properties (*e.g.*, melting point, solubilities) for each *N,N'*-(1,2-dialkoxyethylene)bisamides, utilizing differences in their solubilities in methanol or ethanol. All results are summarized in Table 2.

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Table 1

Run	Acid amide used	React. temp. (°C)	React. time. (hr)	<i>N,N'</i> -(1,2-Dihydroxyethylene)bisamides					
				Formula	Yield (%)	Mp (lit.) (°C)	Anal.	Found	
							C(%)	H(%)	N(%)
1	CH ₃ CONH ₂	60-62	1	(1a)	60	167-169 ^{a)} (166-167) ¹⁾	40.64 40.90	6.93 6.87	15.75 15.90
2	CH ₃ CONH ₂	20-30	50	(1a)	60	168-169 ^{a)} (166-167) ¹⁾	40.92 40.90	6.80 6.87	15.44 15.90
3	C ₆ H ₅ CONH ₂	60-80	1	(1b)	63	169-171.5 ^{b)} (167-169) ¹⁾	63.92 63.99	5.35 5.37	9.38 9.33
4	<i>p</i> -ClC ₆ H ₄ CONH ₂	90	2	(1c)	94	188-192 ^{c)}	51.45 52.05	3.78 3.82	6.93 7.59
5	<i>p</i> -CH ₃ C ₆ H ₄ CONH ₂	80	2	(1d)	92	179-180 ^{b)}	65.62 65.84	6.18 6.14	8.59 8.53
6	CH ₃ (CH ₂) ₁₀ CONH ₂	90	2	(1e)	63	124-127 ^{e)}	68.20 68.37	11.94 11.48	5.88 6.13
7	N  CONH ₂	60-65	0.5	(1f)	82	195-198 ^{c)}	55.91 55.62	4.68 4.67	18.29 18.54
8	2-C ₁₀ H ₇ CONH ₂	75-80	1	—	0	—	—	—	—
9	C ₆ H ₄ (CO) ₂ NH	100	2	—	0	—	—	—	—

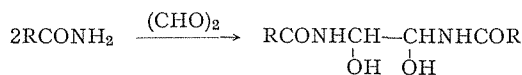
a) Recrystallized from 95 % methanol.

b) Recrystallized from 80 % ethanol.

c) Purified by washing with ethanol.

d) Purified by precipitation from dimethylformamide solution by addition of water.

e) Recrystallized from methanol.


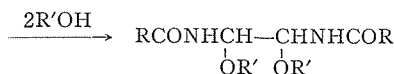

 (1a) R=CH₃,

 (1b) R=C₆H₅,

 (1c) R=*p*-ClC₆H₄,

 (1d) R=*p*-CH₃C₆H₄,

 (1e) R=CH₃(CH₂)₁₀,

 (1f) R=N 

 (2a) R=CH₃; R'=CH₃,

 (2b) R=C₆H₅; R'=CH₃,

 (3a) R=CH₃; R'=C₂H₅,

 (3b) R=C₆H₅; R'=C₂H₅,

Synthesis of 5-Substituted 2,3-Diamido-1,4-dioxanes. The cyclocondensation of the dihydroxybisamide with appropriate glycols, such as ethylene glycol, propylene glycol, and 3-chloro-1,2-propanediol, proceeded smoothly under the presence of *p*-toluenesulfonic acid catalyst. The obtained 2,3-diamido-1,4-dioxanes are tabulated in Table 3. With *N,N'*-(1,2-dihydroxyethylene)bisacetamide (1a), the yield was unusually poor, perhaps it arised from rather high solubility of the product in excess glycol employed in the cyclization reaction.

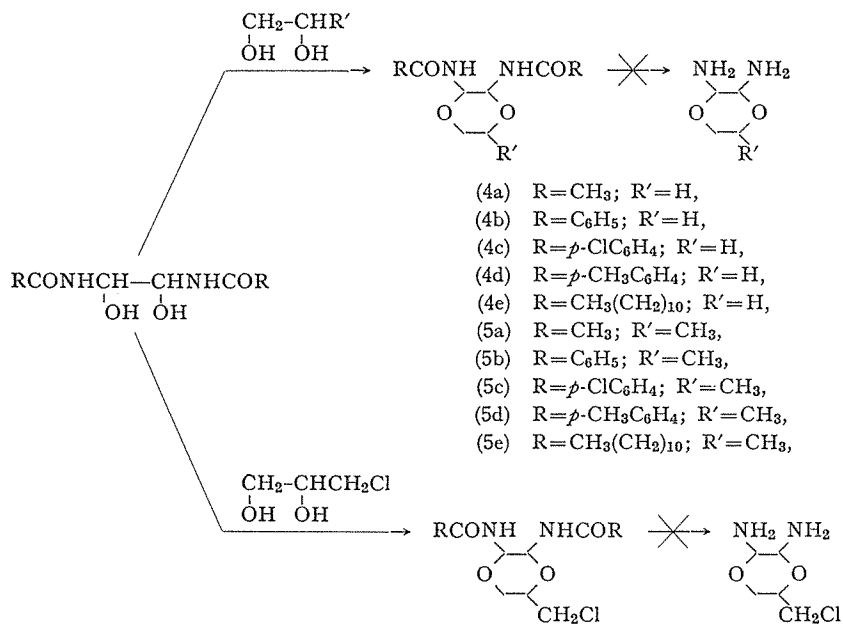
Table 2

Run	Starting material	Alcohol used	Catalyst	React. time (under reflux) (hr)	Formula	<i>N,N'</i> -(1,2-Dialkoxyethylene)bisamides				
						Yield (%)	Mp (lit.) (°C)	Anal.		
								C(%)	H(%)	N(%)
1	(1a)	Methanol	TS ^{a)}	1	(2a)	50 ^{b)}	184–188 ^{f)}	46.72	7.75	13.89
								47.05	7.90	13.72
						36	227–229 ^{f)} (225–226) ¹⁾	46.83	7.90	13.63
2	(1b)	Methanol	H ₂ SO ₄	2	(2b)			47.05	7.90	13.72
						46 ^{e)}	183–186 ^{f)}	65.63	6.22	8.38
								65.83	6.14	8.53
3	(1a)	Ethanol	TS	1	(3a)	40	227–229 ^{f)}	65.74	6.12	8.47
								65.84	6.14	8.53
						35 ^{d)}	201–204 ^{g)}	51.55	8.62	12.13
4	(1b)	Ethanol	TS	2	(3b)			51.70	8.68	12.06
						53	234–237 ^{g)}	51.56	8.85	12.16
								51.70	8.68	12.06
						45 ^{e)}	189–193 ^{g)} (190–191) ⁴⁾	67.30	6.41	7.77
								67.39	6.79	7.86
4	(1b)	Ethanol	TS	2	(3b)			67.39	6.91	7.62
						40	230–232 ^{g)} (219) ⁴⁾	67.52	6.91	7.62
								67.39	6.79	7.86

a) TS; *p*-Toluenesulfonic acid.b) The separation of two stereoisomers was easily effected by the prolonged suspension of the isolated product in methanol (*ca.* 10-times as weighing as crystall). One isomer (50%), which is more soluble in methanol, was obtained by evaporation after filtration, and the other isomer (36%) was collected as filter cake.c), d), e) The above procedure was used, but the following change in solvent was made: for run 2, methanol (*ca.* 100-times in weight); for run 3, ethanol (*ca.* 30-times); for run 4, ethanol (*ca.* 100-times).

f) Recrystallized from methanol.

g) Recrystallized from ethanol.



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- (6a) R=CH₃,
 (6b) R=C₆H₅,
 (6c) R=*p*-ClC₆H₄,
 (6d) R=*p*-CH₃C₆H₄

Unexpectedly, the preparation of diamino-1,4-dioxanes by hydrolysis of diamido-1,4-dioxanes was failed. For example, when 2,3-dibenzamido-1,4-dioxane (4b) was treated with aqueous acid or alkaline (*e.g.*, conc. HCl, 5*N* HCl, or 40% NaOH), any product other than benzoic acid could not be isolated.

Further, a new kind of surfactant was prepared by the reaction of dilauroylamido-1,4-dioxanes (4e and 5e) with propanesultone.

Table 3

Run	Starting material	Glycol used	Catalyst	React. temp. (°C)	React. time (hr)	5-Substituted 2,3-Diamido-1,4-dioxanes					
						Formula	Yield (%)	Mp (lit.) (°C)	Anal.		
									C(%)	H(%)	Found Calcd. N(%)
1	(1a)	EG ^{a)}	TS ^{d)}	80	1.5	(4a)	18	230.5–231.5 ^{f)}	47.58 47.52	7.09 6.98	13.81 13.86
2	(1b)	EG	H ₂ SO ₄	80	1	(4b)	90	257–260 ^{f)} (247–248) ^{g)}	66.04 66.24	5.58 5.56	8.68 8.58
3	(1c)	EG	TS	90	1	(4c)	70	286–288 ^{f)}	54.49 54.70	4.05 4.08	7.07 7.09
4	(1d)	EG	TS	80	2	(4d)	80	266–268 ^{f)}	67.57 67.78	6.36 6.26	7.78 7.91
5	(1e)	EG	TS	140	1	(4e)	67	165–169 ^{g)}	69.41 69.66	11.75 11.28	5.52 5.80
6	(1a)	PG ^{b)}	TS	70–80	0.5	(5a)	58 ^{e)}	226–227 ^{f)}	49.67 49.99	7.52 7.46	12.85 12.96
7	(1b)	PG	H ₂ SO ₄	70–75	3	(5b)	87	264.5–265.5 ^{f)}	66.66 67.04	5.94 5.92	8.15 8.23
8	(1c)	PG	TS	90	1	(5c)	50	261–263 ^{f)}	55.28 55.76	4.34 4.43	6.84 6.85
9	(1d)	PG	TS	80	2	(5d)	68	257–259 ^{f)}	68.64 68.46	6.71 6.57	7.83 7.60
10	(1e)	PG	TS	100	2	(5e)	51	155–157 ^{g)}	69.86 70.11	11.87 11.36	5.34 5.64
11	(1a)	CP ^{c)}	TS	80	1	(6a)	15	251–252 ^{f)}	43.24 43.12	6.12 6.03	11.25 11.18
12	(1b)	CP	H ₂ SO ₄	65–68	0.7	(6b)	65	255–256 ^{f)}	60.60 60.88	5.08 5.11	7.42 7.47
13	(1c)	CP	TS	90	1	(6c)	67	261–262 ^{f)}	51.30 51.43	3.79 3.86	5.85 6.31
14	(1d)	CP	TS	80	2	(6d)	74	270–272 ^{f)}	62.53 62.60	5.81 5.75	6.45 6.95

a) EG; Ethylene glycol.

b) PG; Propylene glycol.

c) CP; 3-Chloro-1,2-propanediol

d) TS; *p*-Toluenesulfonic acid.

e) The product was obtained after vacuum distillation of the reaction mixture.

f) Recrystallized from ethanol.

g) Recrystallized from methanol.

Syntheses of 4,5-Diamido-2-methyl-1,3-dioxolanes and 2-Alkoxy-4,5-diamido-1,3-dioxolanes. The synthesis of 4,5-diamido-2-methyl-1,3-dioxolanes was achieved by the condensation of the dihydroxybisamides with acetaldehyde diethyl acetal, in the presence of *p*-toluenesulfonic acid as a catalyst. Almost identical reaction temperature (90–95°C) was applied in the cyclization to get smooth removal of the alcohol formed during the reaction. All results are summarized in Table 4.

By a similar acid-catalyzed condensation with methyl or ethyl orthoformate, the dihydroxybisamides afforded 2-alkoxy-4,5-diamido-1,3-dioxolanes in high yields, as shown in Table 5.

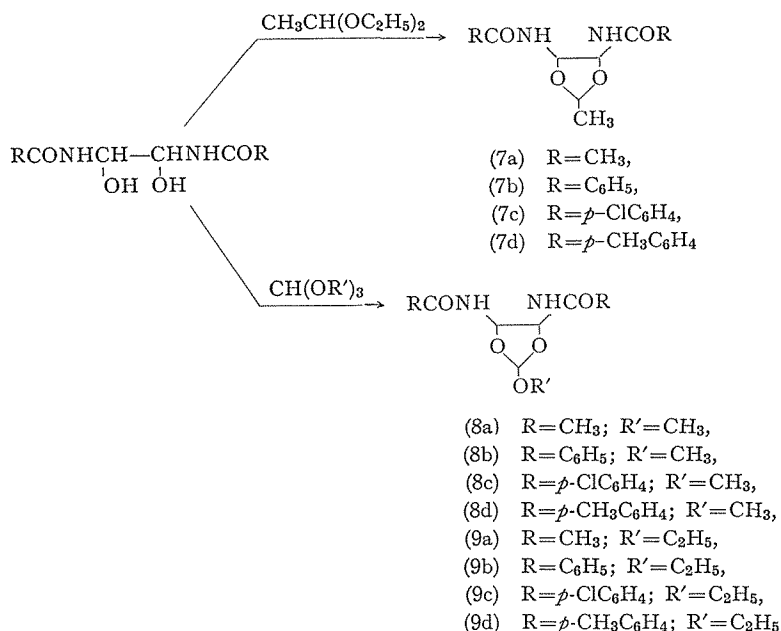


Table 4

Run	Starting material	Catalyst	React. temp. (°C)	React. time (hr)	4,5-Diamido-2-methyl-1,3-dioxolanes					
					Formula	Yield (%)	Mp (°C)	Anal.	Found Calcd.	
								C(%)	H(%)	N(%)
1	(1a)	TS ^{a)}	90	1	(7a)	54	218–222 ^{b)}	47.68 47.52	6.87 6.98	14.07 13.86
2	(1b)	TS	90	1	(7b)	83	233–234 ^{c)}	66.41 66.24	5.82 5.56	8.92 8.58
3	(1c)	TS	90	0.5	(7c)	62	242–245 ^{b)}	54.91 54.70	4.24 4.08	7.06 7.09
4	(1d)	TS	95	0.3	(7d)	64	234–236 ^{b)}	67.60 67.78	6.39 6.26	7.30 7.91

a) TS; *p*-Toluenesulfonic acid.

b) Recrystallized from ethanol.

c) Purified by precipitation from ethanol solution by addition of water.

Table 5

Run	Starting material	Orthoformate used	Catalyst	React. temp. (°C)	React. time (hr)	2-Alkoxy-4,5-diamido-1,3-dioxolanes					
						Formula	Yield (%)	Mp ^{d)} (°C)	Anal. C(%)	Found Calcd. H(%)	N(%)
1	(1a)	MF ^{a)}	TS ^{c)}	80	0.5	(8a)	70	222–223.5	43.95 43.03	6.07 6.47	12.78 12.84
2	(1b)	MF	TS	70–83	0.5	(8b)	90	224–226	63.62 63.15	5.15 5.30	8.39 8.18
3	(1c)	MF	TS	85–90	2	(8c)	90	234–238	52.65 52.57	3.57 3.92	7.01 6.81
4	(1d)	MF	TS	85–90	1	(8d)	88	244–246	64.80 64.85	5.84 5.99	7.51 7.56
5	(1a)	EF ^{b)}	TS	90	0.5	(9a)	88	228–230	46.19 46.54	6.83 6.94	12.00 12.06
6	(1b)	EF	TS	85–100	1	(9b)	91	218–220	63.96 64.03	5.72 5.66	7.44 7.86
7	(1c)	EF	TS	90	1	(9c)	92	215–218	53.38 53.66	4.29 4.27	6.56 6.59
8	(1d)	EF	TS	90–100	1	(9d)	91	217–221	65.45 65.61	6.36 6.29	7.18 7.29

a) MF; Methyl orthoformate.

b) EF; Ethyl orthoformate.

c) TS; *p*-Toluenesulfonic acid.

d) All products were purified by recrystallization from ethanol.

EXPERIMENTAL

For each reaction, only representative examples are given.

The Reaction of Benzamide with Glyoxal. A suspension (adjusted to *pH* 8–9) of benzamide (12.2 g, 0.10 mol), 40% glyoxal (7.3 g, 0.05 mol) and a small amount of NaHCO₃ in water (100 ml) was stirred at 60–80°C for 1 hour. The resulting precipitate was filtered while hot, washed with hot water, dried, and purified (run 3 in Table 1).

The Reaction of (1a) with Methanol. A mixture of (1a) (3 g, 0.017 mol), methanol (40 g, 1.25 mol) and *p*-toluenesulfonic acid (0.1 g) was held at reflux for 1 hour. The mixture was then cooled, and the precipitate was filtered, and recrystallized from methanol. Since the resulting product is a mixture of two stereoisomers, the subsequent operation (see footnote b in Table 2) using methanol was indispensable. The isomer ratio was found to be 50 : 36.

The Reaction of *N,N'*-(1,2-Dihydroxyethylene) bislaurinamide (1e) with Ethylene Glycol. A mixture of (1e) (2.5 g, 0.0055 mol), ethylene glycol (22 g, 0.35 mol) and *p*-toluenesulfonic acid (0.2 g) was stirred at 140°C for 1 hour. The reaction mixture was poured into 300 ml of water under stirring, filtered, and the filter cake was recrystallized from methanol (run 5 in Table 3).

The Reaction of *N,N'*-(1,2-Dihydroxyethylene) bisbenzamide (1b) with Acetaldehyde Diethyl Acetal. To a mixture of (1b) (2 g, 0.0067 mol) and acetaldehyde diethyl acetal (10 g, 0.085 mol) was added dropwise at 90°C a solution of catalyst prepared by dissolving *p*-toluenesulfonic acid (0.1 g) in acetaldehyde diethyl acetal (10 g, 0.085 mol). The resulting mixture was stirred at 90°C for 1 hour under continuous removal of the

ethanol generated in the reaction. At the end of the period of heating, a small amount of water was added to the reaction mixture to remove ethanol easily. After cooling the reaction mixture, the resulting precipitate was filtered and combined with the precipitate obtained by vacuum distillation of the filtrate (run 2 in Table 4).

The Reaction of (1b) with Methyl Orthoformate. A mixture of (1b) (10 g, 0.033 mol), methyl orthoformate (80 g, 0.75 mol) and *p*-toluenesulfonic acid (0.5 g) was stirred at 70–83°C for 0.5 hour under continuous removal of the methanol generated in the reaction. After cooling the reaction mixture to room temperature, the resulting precipitate was filtered and then recrystallized from ethanol (run 2 in Table 5).

The Preparation of Surfactants from Dilauroylamido-1,4-dioxanes and Propanesultone. A mixture of (4e) (3 g), propanesultone (3 g) and NaOH (3 g) was stirred at 150°C for 1 hour. The reaction mixture was poured into water and then filtered. Saturated NaCl aqueous solution was added in one portion to the filtrate and then the precipitated salt (a surfactant) was collected (2.2 g, yield 46%).

Anal. Found: N(%) 3.01. Calcd. for $C_{34}H_{64}N_2Na_2O_{10}S_2$: N(%) 3.63.

A mixture of (5e) (2.7 g), propanesultone (2.7 g) and NaOH (2 g) was stirred at 150°C for 1.5 hours and then worked up in a manner similar to that described above yielding a solid salt (a surfactant) (2 g, yield 51%).

Anal. Found: N(%) 2.88. Calcd. for $C_{35}H_{66}N_2Na_2O_{10}S_2$: N (%) 3.56.

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